OBSERVATIONS ON THE EFFECTS OF DECABORANE AND SEVERAL POTENTIAL ANTIDOTES IN THE RAT

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FOREWORD

This study was accomplished in the Physiological Chemistry Section, Biosciences Branch, under task No. 775305. The paper was submitted for publication on 10 August 1967.

The animals involved in this study were maintained in accordance with the "Guide for Laboratory Animal Facilities and Care" as published by the National Academy of Sciences—National Research Council.

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This report has been reviewed and is approved.

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ABSTRACT

Rats were injected intraperitoneally with decaborane ($B_{10}H_{14}$) and observed over a seven-day period to determine their toxic reactions, including death rate. Pyridoxine, pyridoxal, and pargyline (MO-911) were tested in the decaborane-treated rats as antidotes for the observed manifestations of the boron hydride injection. In these studies pyridoxine (1 mmole/kg.) given simultaneously with decaborane prevented the convulsions and hyperactivity usually seen in rats treated with decaborane alone (20 mg./kg.) and caused a significant decrease in the number of deaths. Pargyline, 50 mg./kg., given with the decaborane gave no significant alteration of the CNS symptoms, but significantly reduced the mortality rate. Pyridoxal phosphate and a higher level of pyridoxine (2 mmoles/kg.) were without beneficial effect. Some implications of the data are discussed.

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I. INTRODUCTION

Boron hydrides have been in use for a number of years as chemical reagents. More recently, further interest in their properties has been generated by their application as high-energy fuels and rocket propellants. Because of the hazards to individuals working with boranes, a number of studies have been published concerning their toxicity and the problems of proper handling of these materials. Such reports have indicated that significant hazards exist with decaborane ($B_{10}H_{14}$) by all practical routes of exposure (1, 2). The vapor pressure of decaborane (and most other boron hydrides) is sufficient to quickly reach toxic concentrations in an enclosed space. Workers accidentally exposed to decaborane suffered from signs and symptoms of nervous system toxicity such as dizziness, weakness, headache, tremors, and involuntary contractions of skeletal muscles (3, 4). Rats exposed to decaborane vapors exhibited nervousness, unsteadiness, slight convulsions, ataxia, and shaking motions of the head (5). In dogs, repeated administration of gelatin capsules containing decaborane at a dosage level of 3 mg./kg. caused listlessness, nervousness, ataxia, vomiting, and tremors of the head (8). These and other observations have illustrated that the most prominent symptoms of decaborane toxicity have been those related in some way to the central nervous system; these include sedation, irritability, and convulsions.

Because many of these symptoms are similar to those obtained with reserpine treatment, several studies have been published to offer evidence that changes in tissue biogenic amine metabolism following decaborane exposure are similar to those seen in animals treated with reserpine. As a result of these findings, many of the efforts to obtain antidotes for decaborane have centered on the monoamine oxidase inhibitors and the index of effectiveness of a given drug as a decaborane antidote has often been its ability to moderate the reserpine-like CNS symptoms and to prevent the depletion of biogenic amines (6).

The assumption, however, of a direct relationship between the CNS effects and the most important toxic reaction, death, does not seem to be supported by previously published data. The purpose of this study, therefore, was to monitor the behavioral changes in animals treated with decaborane and various antidotes and to correlate this subjective information with the objective data gained from the mortality rate. It is hoped this information may prove useful in the evaluation of past studies of decaborane and in the design of future experiments.

II. SUMMARY

Rats injected intraperitoneally with decaborane, 20 mg./kg., became convulsive, ataxic, and alternately hyperactive and sedated; the majority (69%) died within a seven-day period. Pyridoxine, pyridoxal, and pargyline (MO-911) at various dosage levels were tested as antidotes for the decaborane. The hyperactivity and convulsions demonstrated by rats treated with decaborane alone could be alleviated by the simultaneous injection of 1.0 mmole/kg. of pyridoxine; this treatment also caused a significant reduction ($P < .01$) in the seven-day mortality rate. Treatment of decaborane-injected rats with pyridoxal or with a higher

dosage of pyridoxine gave no beneficial results. Rats injected with decaborane plus MO-911 showed no significant reduction in CNS manifestations, although the seven-day mortality rate was significantly reduced ($P = .036$). These studies of the various antidotes fail to demonstrate any positive correlation between the alleviation of CNS symptoms and the reduction in mortality rate.

III. METHODS

Male Sprague-Dawley rats (250 to 350 gm.) were used in this study. They were injected intraperitoneally with various combinations of decaborane (in corn oil), pyridoxine (in normal saline or 27 mM sodium bicarbonate, pH 7.5), pyridoxal (in 0.5% methylcellulose), and MO-911 (in normal saline) (table I). The rats

TABLE I

Injection protocol

Group	Dosage	Drug	Medium	Type injection	Number of rats dead/studied
I	20 mg./kg.	Decaborane	Corn oil	Single	31/45
II	20 mg./kg. + 2 mmoles/kg.	Decaborane Pyridoxine	Corn oil Sodium bicarbonate	Simultaneous	36/45
III	20 mg./kg. + 2 mmoles/kg.	Decaborane Pyridoxine	Corn oil Sodium bicarbonate	30 minutes posttreatment	9/15
IV	20 mg./kg. + 2 mmoles/kg.	Decaborane Pyridoxine	Corn oil Sodium bicarbonate	30 minutes pretreatment	13/15
V	20 mg./kg. + 1.5 mmoles/kg.	Decaborane Pyridoxine	Corn oil Sodium bicarbonate	Simultaneous	9/15
VI	20 mg./kg. + 1 mmole/kg.	Decaborane Pyridoxine	Corn oil Sodium bicarbonate	Simultaneous	3/15
VII	2 mmoles/kg.	Pyridoxine	Sodium bicarbonate	Single	0/15
VIII	20 mg./kg. + 50 mg./kg.	Decaborane MO-911	Corn oil Saline	Simultaneous	6/15
IX	20 mg./kg. + 2 mmoles/kg.	Decaborane Pyridoxal	Corn oil 0.5% methylcellulose	Simultaneous	9/15
X	50 mg./kg.	MO-911	Saline	Single	0/15
XI	15 mg./kg.	Decaborane	Corn oil	Single	2/15
XII	15 mg./kg. + 2 mmoles/kg.	Decaborane Pyridoxine	Corn oil Sodium bicarbonate	Simultaneous	3/15

were given free access to water and Purina Chow prior to and during the course of the study. Following injection with the test material, the animals were observed closely over the first 8-hour period and then at frequent intervals for seven days. The rats were examined for level of physical activity, muscle tremors, muscular coordination, convulsive seizures, startle reaction (by tapping on the cage with a metal bar), and general physical condition.

The death rate in each group of animals was recorded, and the rate in each group compared to that of every other group by constructing 2 x 2 contingency tables. The actual probability for each of these contingency tables was calculated by the formula

$$\text{Probability (P)} = \frac{(a+b)!\,(c+d)!\,(a+c)!\,(b+d)!}{a!\,b!\,c!\,d!\,n!}$$

as given in reference 7.

It is recognized that some comparisons are more meaningful or are of greater interest than others. Nevertheless, for completeness as well as for ease of reporting, the results of all comparisons are shown. Note, however, that only those P values less than .1 are given in table II.

IV. RESULTS

The data obtained by the observations can perhaps be best presented by describing separately the reactions of each group of treated animals (table I). The death rate of each group and its probability are given in table II.

Group I (decaborane alone, 20 mg./kg. of body weight)

Thirty minutes after injection of the decaborane the animals were deeply sedated and inactive. They seemed to have a higher threshold to touch and sound, but when startled by a loud noise they often behaved erratically and were convulsed. This hyperactivity lasted from 80 to 90 seconds and was followed by a deep sedation. Four hours later the animals were still sedated and they reacted sluggishly to sound and touch. However, when aroused they were quite irritable and aggressive. Several animals were noted to be ataxic during this period. Eight hours after injection the animals were still lethargic and remained quiet when undisturbed. Their reaction to sound and touch seemed below normal, and they exhibited sporadic involuntary muscular contractions and an unsteady gait. Marked pilo-erection was present in all the animals. When the animals were startled by sound, they became irritable and aggressive, often fighting among themselves. Within 24 hours the animals were less aggressive and irritable when disturbed by noise and their activity increased, although it was still considerably less than that of the controls. A few animals had bloody discharges from the eyes and nares. After one week of observation, the animals continued to demonstrate decreased activity and lethargy. Thirty-one of the 45 animals treated in this group died; 10 died within 24 hours after injection, 22 within 48 hours, 25 within 72 hours, 29 within 96 hours, and 31 within 120 hours after the injection of 20 mg./kg. decaborane intraperitoneally.

Group II (decaborane, 20 mg./kg., plus simultaneous pyridoxine, 2 mmoles/kg.)

The rats were similar in reaction and behavior to those in group I. The only observed difference was that spontaneous convulsions in group II were rare, but were readily induced by tapping on the cage. At the end of one week, only 9 animals survived of the 45 injected; 20 animals died within the first 24 hours after injection, and 36 within 48 hours after the first injection. The survivors continued to demonstrate decreased activity at the end of the week.

Group III (decaborane, 20 mg./kg., and posttreatment with pyridoxine, 2 mmoles/kg.)

The 15 treated animals used in this observation demonstrated reactions similar to reactions of group II animals. The only significant

TABLE II

*Mortality rate in animals treated with decaborane or the various antidotes**

Group	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	Number of rats dead/studied
I	.094	—	—	—	.001	<.001	.036	—	<.001	<.001	.001	31/45
II		.084	—	.014	<.001	<.001	.005	.084	<.001	<.001	<.001	36/45
III			.090	—	.026	<.001	—	—	<.001	.009	.026	9/15
IV				.090	<.001	<.001	.001	.090	<.001	<.001	<.001	13/15
V					.026	<.001	—	—	<.001	.009	.026	9/15
VI						—	—	.026	—	—	—	3/15
VII							.008	<.001	—	—	—	0/15
VIII								—	.008	.090	—	6/15
IX									<.001	.009	.026	9/15
X										—	—	0/15
XI											—	2/15

*Each group was compared with every other group by means of a 2 x 2 contingency table and the actual probability (P) for each pair calculated by

$$P = \frac{(a+b)!\,(c+d)!\,(a+c)!\,(b+d)!}{a!\,b!\,c!\,d!\,n!}$$

Those values of $P < .1$ are given in the table

difference observed between the animals injected simultaneously with pyridoxine (group II) and this group of "postinjected" animals (2 mmoles pyridoxine/kg. 30 minutes after the decaborane) was that the latter group exhibited no convulsive seizures and the death time was prolonged. Nine of the 15 treated animals died during the one-week observation period, with 5 deaths occurring within 36 hours of injection, 7 within 48 hours, and a total of 9 within the seven-day observation period. The six animals that survived for one week showed decreased activity and had a small amount of bloody discharge from the eyes and nares.

Group IV (decaborane, 20 mg./kg., and pretreatment with pyridoxine, 2 mmoles/kg.)

Pretreatment of the 15 animals with pyridoxine 30 minutes prior to the decaborane injection caused no changes in the optimum time of convulsion (normally 30 minutes after the injection of decaborane) and did not alter the usual hyperactivity. Four hours after injection the animals had a very unsteady gait and were sedated and ataxic. Twenty-four hours after injection their activity was far below that of the controls and they remained ataxic and anorexic. Within the week, 18 animals died, of 15 that were treated; 7 deaths occurred within 24 hours after injection, 9 within 30 hours, 12 within 48 hours, and the 18th animal died six days after injection. After the animals had been observed for one week, the condition of the two survivors was similar to that of rats in group III.

Group V (decaborane, 20 mg./kg., plus simultaneous pyridoxine, 1.5 mmoles/kg.)

The 15 animals that were injected with a lower dosage level of pyridoxine (1.5 mmoles/kg.) were well sedated within 30 minutes after the injection of decaborane (20 mg./kg.). By periodically observing this group of animals for 24 hours following injection, it was seen that they demonstrated reactions similar to those shown by animals in groups III and IV, although they had no convulsions. At the end of one-week observations, 9 animals had died and 6 survived; 2 animals died within 24 hours after injection, 5 within 36 hours, 6 within 72 hours, 7 within 96 hours, 8 within 120 hours, and the ninth animal died on the sixth day after treatment. The survivors after one week exhibited activity that was judged slightly below normal.

Group VI (decaborane, 20 mg./kg., plus simultaneous pyridoxine, 1.0 mmole/kg.)

The 15 animals injected at this level of pyridoxine were depressed 30 minutes after the injection but did not display any convulsions during the one-week observation period. Piloerection and sedation were observed in all animals and several exhibited mild conjunctival hemorrhages, but these were significantly reduced when compared with the treated animals in the first three groups. Within 24 hours, this group of animals showed more spontaneous activity than any other group of animals injected with decaborane in combination with pyridoxine. Only 8 animals died within the one-week observation period; the mortality rate in this group of animals was significantly lower ($P < .001$) compared to groups I, II, III, IV, and V.

Group VII (pyridoxine alone, 2 mmoles/kg. of body weight)

Within one hour the animals' activity and reaction to sound and touch were far below normal. This mild sedation, together with some unsteadiness of gait, lasted about 4 hours before slowly subsiding over the subsequent 24-hour period. At the end of one week, no deaths had occurred in this group of 15 animals. Their physical condition was normal and they demonstrated no effects of the injection.

Group VIII (decaborane, 20 mg/kg., plus simultaneous MO-911, 50 mg./kg.)

Thirty minutes after injection the animals were sprawled in the cage in an irregular position, deeply sedated and inactive. The animals evidently could not walk; they exhibited convulsive seizures and erratic behavior at the

slightest provocation. Four hours after injection the animals were still sedated and had pilo-erection, ataxia, and dulled responses to sound and touch. When aroused, however, the animals were aggressive and became irritable when touched. Eight hours after injection the animals showed more activity, although this was well below that of the controls. Several animals gave evidence of abdominal pain and discomfort, possibly as a result of a local reaction to the intraperitoneal injections. All other symptoms were similar to those that existed 4 hours after injection. Twenty-four hours after injection this group of animals was only slightly less active than the controls. Their gait was steady, and they responded in a normal manner to sound and touch. The animals did not demonstrate pilo-erection or ataxia, but several had a mild hemorrhage around the nares. Of the 15 animals treated, 6 died during the seven days; 3 animals died within 48 to 54 hours after injection, 5 within 72 hours after injection, and 6 within 96 hours after injection. The death rate was lower than that of groups I ($P = .036$), II ($P = .005$), and V ($P = .001$) and not significantly different ($P = .162$) from that of group VI which was treated with 1 mmole pyridoxine plus 20 mg. decaborane/kg.

Group IX (decaborane, 20 mg./kg., plus simultaneous pyridoxal, 2 mmoles/kg.)

The reactions and behavior of these animals were not different in any respect from those receiving 20 mg. decaborane alone (group I). The sedation, irritability, and convulsions all appeared in the expected intensity. After a week, the survivors appeared to be unconcerned about food and water and showed a decrease in spontaneous activity. Nine animals died, of the 15 injected; 2 of the animals died within 24 hours after injection, 4 within 30 hours, 8 within 96 hours, and 9 within 120 hours after injection.

Group X (MO-911, 50 mg./kg. of body weight)

Thirty minutes after injection all 15 rats appeared to be very mildly sedated and exhibited a decrease in activity. Reaction to sound and touch was diminished. Three to 5 hours after injection the animals became hyperactive, alert, inquisitive, and had very good reaction to sound and touch. Within 24 hours after injection their activity and responses had returned to normal and they demonstrated no continuing ill effects from the injection. At the end of one week, no deaths had occurred in this group of animals, and no difference could be observed between this group and the control animals.

Group XI (decaborane alone, 15 mg./kg.)

The animals were only mildly sedated within 30 minutes after the injection. There were no spontaneous convulsions in this group nor could they be induced. Within 4 hours the animals had a decrease in activity and an unsteady gait. Twenty-four hours later their activity had increased but was still significantly less than that of the controls. Several animals had mild conjunctival hemorrhages. Two of the 15 animals injected died. The survivors showed no residual ill effects.

Group XII (decaborane, 15 mg./kg., plus simultaneous pyridoxine, 2 mmoles/kg.)

This group of 15 animals was injected simultaneously with pyridoxine and the lower dosage (15 mg./kg.) of decaborane. There were no convulsions, but the animals were very mildly sedated within 30 to 45 minutes. The overall reaction was judged to be the same as for animals receiving the same amount of decaborane alone (group XI). At the end of seven days 3 animals had died. The survivors demonstrated no ill effects from the treatment.

V. DISCUSSION

Rats injected with decaborane alone (20 mg./kg.) demonstrated sedation, ataxia, and convulsions, and the majority (69%) died within a seven-day period. It has been shown in this laboratory that this dosage of decaborane causes 100% depletion of brain norepinephrine within 24 hours (6). Pyridoxine, at the level of 1 mmole/kg., given simultaneously, limited this depletion to only

50% while pyridoxine, in the dosage of 2 mmoles/kg., completely obviated depletion of brain norepinephrine (9). Similar, though not so striking, dose responses to pyridoxine were seen in the heart norepinephrine levels (9). These and other data of the same sort naturally have been used as criteria in selecting suitable antidotes for decaborane and indeed served as guidelines for the design of the present study.

As one might have predicted from the results of earlier studies (6, 9), the decaborane-treated rats injected with only 1 mmole/kg. pyridoxine (group VI) were less sedated, had no convulsions, and returned to their normal activity more quickly than those rats treated with decaborane alone. Moreover, the death rate was significantly lower ($P = .001$) in those rats simultaneously given 1 mmole/kg. pyridoxine. On the other hand, this study demonstrates that 2 mmoles/kg. of pyridoxine, whether given prior to (group IV), with (group II), or following (group III) the decaborane, effects no significant change in either the behavior or death rate. On the contrary, the rats were sedated, ataxic, and convulsive, and of the 75 rats making up groups II, III, and IV, 77% died. This paradoxical effect is most surprising in view of the manifest dose-related beneficial effects of pyridoxine upon brain and heart biogenic amines. The data, however, may be interpreted as demonstrating an interesting dichotomy between biogenic amine metabolism and decaborane lethality. Recent studies of pyridoxal-requiring enzymes in this laboratory clearly demonstrate that other vital enzyme systems may be more important in decaborane toxicity than those of amine metabolism (10); the present data may represent further evidence of the same nature.

Furthermore, if one assumes that the pyridoxine acts directly as an antidote (or as a replacement for pyridoxine destroyed by the boron hydride), then one would expect pyridoxal to be just as effective in subverting the lethality of decaborane, since it has been shown in vitro that pyridoxal phosphate is as effective as pyridoxine for transamination reactions (11). In addition, only the pyridoxal analog is effective as a cofactor for the decarboxylating enzymes so important in amine metabolism. Thus, if one assumes that the primary role of pyridoxal and its analogs in alleviating the effects of decaborane rests merely in the straightforward replacement of pyridoxal cofactor, there are a number of reasons for expecting pyridoxal to be as effective as pyridoxine. This is not the case; pyridoxal was not useful in preventing the CNS effects and the death rate of animals treated with 2 mmoles/kg. pyridoxal simultaneously with the 20 mg./kg. decaborane was the same as that of the rats receiving only decaborane. This paradoxical ineffectiveness of pyridoxal in these experiments is paralleled by its inability even to prevent depletion of the brain biogenic amines in this laboratory (6). One possibility is the proposed differing cell permeability properties of the two forms of B_6 (10). However, this speculation does not explain the lack of a dose-response relationship in the pyridoxine-treated groups (IV, V, and VI).

Administration of a slightly lower level of decaborane (15 mg./kg. together with 2 mmoles/kg. of pyridoxine (group XII)) gave results similar to those obtained with 15 mg./kg. decaborane alone (group XI) and with 20 mg./kg. decaborane and 1 mmole/kg. pyridoxine (group VI). These data may be interpreted as evidence against a toxic effect of the 2 mmoles/kg. pyridoxine itself. Further evidence that pyridoxine itself is not toxic is given by group VII, where the injection of pyridoxine (2 mmoles/kg.) alone resulted in no deaths and only relatively minor effects consisting of some mild sedation and unsteadiness of gait during the first 24-hour period.

The other drug tested in this study, pargyline, is a nonhydrazide monoamine oxidase inhibitor. It has been shown that this compound almost completely prevents the depletion of brain norepinephrine caused by decaborane (6); the effect is similar to that obtained with high doses of pyridoxine. The present study demonstrates further that pargyline, 50 mg./kg., given simultaneously with 20 mg./kg. decaborane (group VIII), has a protective action against decaborane in terms of significantly lowering ($P = .036$) the

incidence of death as compared to that caused by decaborane alone; this protection is not different ($P = .159$) from that obtained with 1 mmole pyridoxine. However, pargyline treatment was not associated with any significant reduction in seizures, sedation, or the other CNS effects usually associated with decaborane toxicity. Indeed, this seems to illustrate once more that the CNS symptoms (and brain amine levels) may not be directly associated with the lethality of decaborane.

In sum, this study has described the toxic and lethal effects of decaborane in the rat as well as the efficacy of pyridoxine and pargyline (and the ineffectiveness of pyridoxal) in reducing and preventing these manifestations. We feel these data are especially intriguing since they do suggest that the primary protective benefits derived from drugs enhancing biogenic amine metabolism of the brain may not be directly related to this metabolic role, and that it may prove more fruitful to examine other metabolic systems. Hopefully, studies in progress will help to clarify the role of pyridoxine and its analogs in some of these enzyme systems and thus help in the treatment of boron hydride reactions.

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13. ABSTRACT: Enter an abstract giving a brief and factual summary of the document indicative of the report, even though it may also appear elsewhere in the body of the technical report. If additional space is required, a continuation sheet shall be attached.

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